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Applicants	: Lindberg et al.	
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John M Genova — 11/12/99
Signature — Date of Signature

Commissioner of Patents and Trademarks
Washington, D.C. 20231

LETTER

Sir:

Applicants submit this Letter and the accompanying Declaration of Tommy Andersson under 37 C.F.R. §1.132, Information Disclosure Statement and Terminal Disclaimer in support of the patentability of the claimed invention vis-à-vis the prior art of record.

REMARKS

I. Lineage of Referenced Application

The referenced application is a continuation of U.S. Patent Application Serial No. 08/899,931, filed July 24, 1997, now abandoned (the "'931 application"), which is a continuation of U.S. Patent Application Serial No. 08/376,512, filed January 23, 1995, now U.S. Patent No. 5,714,504, issued February 3, 1998 (the "'504 patent"), which is a continuation-in-part of U.S. Patent Application Serial No. 08/256,174, filed June 28, 1994 as a 35 U.S.C. §371 application of PCT/SE94/00509, filed May 27, 1994, now U.S. Patent No. 5,693,818, issued December 2, 1997 (the "'818 patent").

II. Description of Invention and Pending Claims

Claims 35-51 are pending in the application. Claims 35-41 and 50 are directed to a pharmaceutical formulation for parenteral administration comprising a pure solid state alkaline salt of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole as the active ingredient and a pharmaceutically acceptable carrier. Claims 42-49 and 51 are directed to methods of treating gastrointestinal inflammatory disease and inhibiting gastric acid secretion comprising the parenteral administration of a pure solid state of the (-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, in either its non-salt or alkaline salt form, as the active ingredient and a pharmaceutically acceptable carrier. For ease of discussion in this Letter, the generic name "omeprazole" will be used hereinafter for the compound 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

As disclosed on page 11, lines 6-11 of the subject application, the processes used to obtain the optically pure sodium salt of the (-)-enantiomer of omeprazole result in a change of direction from the (-) to the (+) optical rotation when prepared from the neutral form of the (-)-enantiomer of omeprazole. Thus, the optical rotation of the neutral form of the (-)-enantiomer of omeprazole has a negative direction (See, Example 12, Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole: $[\alpha]_D^{20}$ -155° (c=0.5%, chloroform)), whereas the sodium salt of the (-)-enantiomer has a positive direction (See, Example 1, Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt: $[\alpha]_D^{20}$ +42.8° (c=0.5%, water)).

Similarly, the process used to obtain the optically pure magnesium salt of the (-)-enantiomer of omeprazole results in a change of direction from the (+) to the (-) optical rotation when prepared from the sodium salt of the (-)-enantiomer. Thus, the rotation of the magnesium salt of the (-)-enantiomer of omeprazole has a negative direction (See, Example 5, Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium salt: $[\alpha]_D^{20}$ -128.2° (c=1%, methanol).

This phenomenon is also reported by Sverker von Unge et al., "Stereochemical assignment of the enantiomers of omeprazole from X-ray analysis of a fenchyloxymethyl derivative of (+)-(R)-omeprazole", Tetrahedron: Asymmetry, Vol. 8, No. 12, pp. 1967-1970, 1997. Specifically, von Unge et al. disclose that the sign of the optical rotation is reversed in relation to that of the neutral form when the measurement of the optical rotation is performed with the enantiomers of omeprazole as sodium salts dissolved in water. Thus, the R-enantiomer as the sodium salt has the optical rotation $[\alpha]_D^{20}$ -44.1° (c=0.5%, water), whereas the R-enantiomer in neutral form has the optical rotation $[\alpha]_D^{20}$ +181.5° (c=0.5%, chloroform).

Notwithstanding the change in optical rotation as discussed, the absolute configuration of the compound remains the same. A copy of the von Unge et al. article is submitted concurrently with this Letter as part of the accompany Information Disclosure Statement.

III. Procedural History

In the parent '931 application, a final Office Action was mailed on September 18, 1998 according to which the pending claims were rejected on various grounds. Specifically, claims 35-51 were rejected under 35 U.S.C. §102(b) as being anticipated by DE 4,035,555 ("DE '455"). Claims 35-51 were also rejected under 35 U.S.C. §103(a) as being unpatentable in view of the combination of DE '455 and CA 117:90292. Claims 35-41 were rejected under 35 U.S.C. §101 as claiming the same invention as that of the '504 patent. Claims 42-49 and 51 were rejected for obviousness-type double patenting reasons in view of the '504 patent.

In response to the novelty and obviousness rejections in the parent '931 application, Applicants submitted a copy of the Declaration that had been submitted pursuant to 37 C.F.R. §1.132 in the application underlying the grandparent '504 patent. However, the Examiner stated in the final Office Action that the previously submitted Declaration was relevant only for the ***oral administration*** of pharmaceutical formulations comprising an alkaline salt of the (-)-enantiomer of omeprazole as the active ingredient.

IV. Comparative Data Supporting Patentability of Parenteral Administration

Applicants have completed a clinical study comparing the pharmacokinetics after ***intravenous administration*** of the sodium salt of the (-)-enantiomer of omeprazole and the sodium salt of omeprazole racemate. A description of the comparative study and a summary of the results are set forth in the accompanying Declaration of Tommy Andersson.

Individuals taking omeprazole can be classified according to the rate by which the body metabolizes the drug. The rate at which the body is able to metabolize omeprazole is genetically determined. So-called rapid or normal metabolizers possess the genetic make-up to express the enzyme CYP2C19 that is mainly responsible for metabolizing omeprazole. Conversely, the enzyme CYP2C19 is not expressed in so-called slow or poor metabolizers. This difference in metabolic ability leads to measurable differences in plasma levels of omeprazole between rapid and slow metabolizers which ultimately translates into interindividual variations during treatment with omeprazole.

In accordance with the comparative study, 40 mg of the sodium salt of the (-)-enantiomer of omeprazole and 40 mg of the sodium salt of the omeprazole racemate were administered intravenously to thirteen rapid metabolizers and two slow metabolizers. The plasma levels of the compounds were measured after single and repeated doses. The data appears in the Table and Figures 1-3 of the Declaration of Tommy Andersson.

With respect to the rapid metabolizers, it was found that the mean plasma concentration versus time curve (AUC) after both single and repeated intravenous doses of the sodium salt of the (-)-enantiomer of omeprazole was almost 40% higher than that of the sodium salt of omeprazole racemate (See, Declaration, Table). Since the inhibitory effect on gastric acid secretion of omeprazole or its enantiomers is directly correlated to the AUC, the results

demonstrate the potential for a more pronounced inhibitory effect on gastric acid secretion by the (-)-enantiomer of omeprazole compared to the racemate.

With respect to the slow metabolizers, it was found that the AUC of the (-)-enantiomer of omeprazole after a single intravenous dose of the sodium salt was 2.5-2.9 times greater in slow metabolizers than in rapid metabolizers. With the sodium salt of omeprazole racemate, the difference in AUC between slow and rapid metabolizers after a single intravenous dose was approximately 4.6-5.0 times. Corresponding differences between slow and rapid metabolizers after repeated dosing were less, approximately 1.5 times greater and 3 times greater for the sodium salt of the (-)-enantiomer of omeprazole and the sodium salt of omeprazole racemate, respectively.

In summary, therefore, the data submitted in the Declaration of Tommy Andersson demonstrates that there are two advantageous properties with the intravenous administration of an alkaline salt of the (-)-enantiomer of omeprazole compared to an intravenous administration of an alkaline salt of omeprazole. These therapeutic advantages include a higher AUC in a majority of the population and a reduced interindividual variation among patients. As a result, optimal plasma concentrations of the drug with the desired gastric acid anti-secretory effect are possible in a larger fraction of patients. The more advantageous pharmacokinetic profile of the (-)-enantiomer of omeprazole in terms of plasma concentrations and interindividual variation is unexpected in view of the conclusions reported in the publication by Cairns, A. et al. "Enantioselective high-performance liquid chromatographic determination of omeprazole in human plasma", Journal of Chromatography B, 666 (1995) 323-328. A copy of the Cairns et al. article was submitted as part of an Information Disclosure Statement, mailed February 3, 1997, in the application underlying the great-grandparent '818 patent.

The later publication date of the Cairns et al. article disqualifies that article as prior art. Nevertheless, Applicants submit that the Cairns et al. article is representative of the state of the art at the time the invention was made. Specifically, Cairns et al. measured the concentrations of (+)-enantiomer and (-)-enantiomer of omeprazole after the intravenous administration of a 20 mg dose of omeprazole racemate. Cairns et al. reported that, when a racemic dose of omeprazole is administered intravenously, the concentration of (+)-omeprazole and (-)-omeprazole were essentially equal in the plasma samples that were assayed. Thus, at the time the invention was made, the person of ordinary skill in the art would have expected the pharmacokinetic profile of the omeprazole racemate and of each enantiomer to be essentially the same.

Applicants submit that the data and conclusions set forth in the instant Declaration of Tommy Andersson are consistent with data and conclusions of the Declaration submitted in the grandparent '504 patent claiming the oral administration of pharmaceutical formulations comprising an alkaline salt of the (-)-enantiomer of omeprazole.

V. Novelty Rejection under 35 U.S.C. §102(b)

In the parent '931 application, claims 35-51 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by DE 4,035,455. It is established law that anticipation requires the disclosure in a single prior art reference of each and every element of the claimed invention. Furthermore, anticipation requires that the prior art reference must "teach", thus placing the allegedly disclosed subject matter in the possession of the public.

The active ingredient of the claimed invention is the pure (-)-enantiomer of omeprazole which is administered parenterally preferably in the form of its alkaline salt. The instant Declaration of Tommy Andersson demonstrates that the (-)-enantiomer of omeprazole,

administered as the sodium salt, has a different and more advantageous pharmacokinetic profile in terms of a higher AUC and lower interindividual variation when compared to the omeprazole racemate, also administered as a sodium salt.

The DE '455 reference discloses both the (+)-and (-)-enantiomer of omeprazole at page 9, lines 29-32, and their salts with bases at page 10, line 1. However, the reference does not "teach" that the (-)-enantiomer of omeprazole could have pharmacokinetic properties making the (-)-enantiomer a more efficacious and desirable medicament in the treatment of gastric and intestinal disorders by parenteral administration. Moreover, the reference fails to provide a single working example directed to the preparation of a pure solid state alkaline salt of the (-)-enantiomer of omeprazole. As such, the DE '455 reference is not enabling and, therefore, does not place the claimed invention in the possession of the public.

For all of the foregoing reasons, claims 35-51 of the subject application are not anticipated by DE '455.

VI. Obviousness Rejection under 35 U.S.C. §103(a)

Claims 35-51 of the parent '931 application were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over DE '455 in view of CA 117:90292. The primary reference DE '455 discloses the non-salt form of the (+)- and (-)-enantiomer of omeprazole. The secondary reference discloses a method for preparing alkali metal salts of omeprazole in the racemic form.

The comparative data submitted in the Declaration of Tommy Andersson shows that the (-)-enantiomer of omeprazole unexpectedly exhibits a different and more advantageous pharmacokinetic profile than the omeprazole racemate. This discovery was contrary to the state of the art which maintained that the concentration of the (+)- and the (-)-enantiomer of

omeprazole, after the intravenous administration of omeprazole racemate, were essentially equal in the plasma samples that were assayed (See, Cairns et al.). Thus, the more advantageous pharmacokinetic profile of the (-)-enantiomer of omeprazole in terms of plasma concentrations and interindividual variation was indeed unexpected.

Neither the primary reference DE '455 or the secondary reference CA 117:90292, whether taken alone or in combination, suggests that an alkaline salt of the (-)-enantiomer of omeprazole would be more efficacious as the active ingredient of a pharmaceutical formulation for parenteral administration than either an alkaline salt of the omeprazole racemate or the (+)-enantiomer of omeprazole.

For all of the foregoing reasons, claims 35-51 of the present application are non-obvious under 35 U.S.C. §103(a) in view of the cited art of record.

VI. Same-Invention Double Patenting Invention Rejection under 35 U.S.C. §101

Claims 35-41 of the parent '931application were rejected under 35 U.S.C. §101 as claiming the same invention as that of the grandparent '504 patent. Applicants submit that the rejection is improper. The '504 patent claims a pharmaceutical formulation for oral administration comprising an alkaline salt of the (-)-enantiomer of omeprazole as the active ingredient. In contrast, the claimed invention is directed to a pharmaceutical formulation ***for parenteral administration*** comprising an alkaline salt of the (-)-enantiomer of omeprazole as the active ingredient. The formulations of the claimed invention must be sterile and sterility is not necessarily a feature of the claimed oral formulations of the '504 patent. Therefore, claims 35-41 and 50 of the present application do not define identically the same invention as the '504 patent.

VII. Obviousness-type Double Patenting Rejection

Claims 42-51 of the parent '931 application were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of the grandparent '504 patent. In order to overcome the rejection, Applicants submit a Terminal Disclaimer whereby they disclaim the terminal part of any patent to be granted in the present application that would extend beyond the expiration date of the '504 patent, even if such a Terminal Disclaimer would have no effect since the patent term of a patent to be granted for the subject application would expire May 27, 2014, i.e., 20 years from the U.S. filing date of great-grandparent '818 patent. In contrast, the patent term of the '504 patent will expire February 3, 2015, i.e., 17 years from the date of grant.

The Assistant Commissioner is authorized to charge Account Deposit No. 23-1703 in the amount of $110.00 in connection with the filing of the Terminal Disclaimer.

CONCLUSION

Claims 35-51 are directed to patentable subject matter. Accordingly, Applicants request reconsideration and allowance of the claims.

Any additional fees due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: November 12, 1999

Respectfully submitted,

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Enclosures
Declaration of Andersson
Terminal Disclaimer
Information Disclosure Statement